Safety and effectiveness of a four-factor prothrombin complex concentrate for vitamin K antagonist reversal following a fixed-dose strategy

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Introduction

There is no doubt that nowadays to reverse the anticoagulant effect of vitamin K antagonists (VKA), such as warfarin and acenocoumarol, prothrombin complex concentrate (PCC) should be used. PCC administration, usually in combination with intravenous vitamin K, tends to rapidly and safely restore haemostasis, when used according to established safety procedures (appropriate dosing, reversal monitoring and, in most cases, no repeated doses).

In this brief introduction, I have mentioned appropriate dosing of PCC for optimal VKA reversal; this is still a controversial topic which has not received enough clarification. Different dosing strategies for VKA reversal have been recommended, including variable dosing based on the baseline international normalised ratio (INR), considered target INR, the patient's weight or underlying pathology, or providing a fixed dose; however, there is no agreement what the "best fixed dose" for all patients is. The article we will discuss today recommends an initial fixed dose of 1000 IU PCC and additional 500 IU doses evaluated on a case-by-case basis based on outcomes after initial administration.

Commentary

The authors justify the study based on the paucity of clinical data demonstrating the efficacy and safety of a fixed-dose strategy compared with manufacturer's dosing recommendations, i.e., 25–50 IU/kg depending on baseline INR. The authors' recommendation is based on their opinion that the proposed strategy is effective and associated with less adverse events, particularly thromboembolic events, than the standard strategy.

This was a retrospective study of adult patients who received four-factor prothrombin complex concentrate (4F-PCC) for VKA reversal. The primary outcome was INR correction, defined as the first INR draw ≤1.5 after 4F-PCC, and the safety outcome was any thromboembolic event within 90 days after 4F-PCC. A total of 145 patients were included in two groups, 106 patients in the bleeding group and 39 patients requiring emergency surgery. The results showed that most patients (70.3%) achieved the target INR. Only one thromboembolic event was reported to be possibly related to 4F-PCC. The authors suggest their fixed-dose strategy is valid and should be considered for VKA reversal.

This is an interesting study, well-structured and well-documented, with a good design, albeit being retrospective. The majority of patients only required one 1000 IU PCC dose to reach the INR target of ≤1.5; however, 33% of patients required an additional 500 IU dose and 7% two or more 500 IU doses. These results demonstrate that only the initial dose should be fixed at 1000 IU, and the response should be monitored and acted on based on whether the proposed target has or not been achieved or whether additional doses are required.

It is important to emphasise that all patients received 10 mg vitamin K concomitant with PCC, demonstrating the importance of supporting VKA reversal with vitamin K supplementation.

The authors highlight that with their suggested strategy similar outcomes to those published in other studies with higher doses can be achieved. In these other studies, doses were calculated based on the baseline INR and did not use an initial fixed PCC dose.

Furthermore, it is worth mentioning the low number of thromboembolic events reported within three months, which is essential to the safety profile of PCC for early VKA reversal.

To conclude, this is an interesting study that demonstrates that an initial fixed dose of 1000 IU PCC with 10 mg intravenous vitamin K, with INR monitoring and, if necessary, additional 500 IU PCC, is a strategy with good efficacy and safety for VKA reversal.